

Protocol Development for HRQOL Clinical Trials

Conference on Quality of Life Research in Asia
May 19, 2006

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Trial Protocol / Phases

- o All clinical trials follow strict scientific guidelines which are outlined in a clinical trial protocol
- o The protocol contains a description of the study's goals, how the new drug will be taken, who will be included in the study, what medical tests will be done, and what data will be collected
- o Each center participating in the study uses the same protocol to help make sure that the information collected from the centers can be combined and compared
- o Clinical trials are usually done in three phases

Phase I Trial

Is it safe in humans?

- o Phase I studies investigate the drug's safety and are conducted with a small number of healthy volunteers
- o These trials are used to evaluate what happens to the drug in the human body
- o MTD (Maximum Tolerated Dose)

Phase II Trial

Does it work in humans?

- o Phase II trials involve a larger number of people and provide information about how well a new drug works, along with additional information about the benefit of the drug and its safety
- o Does the drug have any promising activity?
- o These studies are usually "randomized" and "blinded"
- o Randomized means that one group of patients receives the new drug, while a second "control" group receives either a standard treatment or a placebo (or "sugar pill")
- o Blinded means that neither the patients nor the researchers know who is getting the new drug until the trial is over

Phase III Trial

Is it better than current treatment?

- o Comparative trials showing effectiveness of new treatments
- o Phase III trials expand the testing to include large numbers of people
- o Phase III studies often involve thousands of people and can last for several years
- o These studies provide researchers with a thorough understanding of the new drug's effectiveness, its benefits, and the range of possible side effects
- o Like Phase II trials, Phase III trials are usually randomized and blinded
- o Once Phase III testing is successfully completed, the sponsor will request FDA approval to market the drug

Phase IV Trial

What are the longer term effects, or additional uses for the therapy?

- o After receiving FDA approval for a new drug, sponsors often conduct Phase IV studies (Postmarketing Study or PMS)
- o The focus of these trials is usually to evaluate the long-term benefits of the drug
- o A sponsor may also conduct Phase IV studies to compare the cost-effectiveness of the new drug to traditional treatments

Study Protocol

- Every well-designed clinical trial requires a protocol
- The study protocol can be viewed as a written agreement between the investigator, the participant, and the scientific community
- The contents provide the background, specify the objectives and describe the design and organization of the trial; every detail explaining how the trial is carried out does not need to be included
- The protocol serves as a document to assist communication among those working in the trial
- The protocol should be developed before the beginning of participant enrollment and should remain essentially unchanged except perhaps for minor updates
- Careful thought and justification should go into any changes

Outline of a Typical Protocol (1)

- A. Background of the study
- B. Objectives
 - 1. Primary question and response variable
 - 2. Secondary questions and response variables
 - 3. Subgroup hypotheses
 - 4. Adverse effects
- C. Design of the study
 - 1. Study population
 - a. Inclusion criteria
 - b. Exclusion criteria
 - 2. Sample size assumptions and estimates
 - 3. Enrollment of participants
 - a. Informed consent
 - b. Assessment of eligibility
 - c. Baseline examination
 - d. Intervention allocation (e.g., randomization method)
 - 4. Intervention
 - a. Description and schedule
 - b. Measures of compliance
 - 5. Follow-up visit description and schedule

Outline of a Typical Protocol (2)

- C. Design of the study (cont'd)
 - 6. Ascertainment of response variables
 - a. Training
 - b. Data collection
 - c. Quality control
 - 7. Data analysis
 - a. Interim monitoring
 - b. Final analysis
 - 8. Termination policy
- D. Organization
 - 1. Participating investigators
 - a. Statistical unit or data coordinating center
 - b. Laboratories and other social units
 - c. Clinical center(s)
 - 2. Study administration
 - a. Steering committees and subcommittees
 - b. Data monitoring committee
 - c. Funding organization
- E. Appendix

Introduction (1)

- Considerations for measuring HRQOL in clinical trials
 - Is HRQoL the major (primary) or minor (secondary) outcome (endpoint) being studied?
 - Which method of HRQOL measurement - interview or questionnaire – will be used?
 - To what degree will interviews be constructed?
 - If questionnaires are being used, which questionnaire(s) are best suited for the purpose of the study?
 - What are the eligibility requirements for the HRQOL position of the study, and are these different from the eligibility requirements for the study itself?

Introduction (2)

- Considerations for measuring HRQOL in clinical trials (cont'd)
 - What is the required sample size and how is it to be determined?
 - When will measurements be taken?
 - Where will measurements be taken?
 - How will compliance be documented?
 - How will the measurement be implemented?
 - What should the trial protocol contain about HRQOL assessment?
 - How will the HRQoL assessments be monitored?
 - How will the results be analyzed and reported?

HRQOL Protocol (1)

- Integral part under each headings of the main protocol (Osoba, 1992)
- **Introduction and Background**
 - why is measurement of HRQOL relevant in the trial?
 - Is a hypothesis being tested or is the purpose to provide descriptive data for the generation of hypotheses?
 - How will the results be used after the trial is completed?
 - Will an interview or self-report questionnaire approach be used?
 - Will an interview be open ended or structured?
 - If the questionnaire method is used, which instrument(s) will be used and why was it (were they) chosen for this trial?
 - Literature references must be given to support the choices and the reliability, validity, and responsiveness of the instruments that will be used
 - Answers to all of the above can be provided in a reasonably short paragraph that establishes the background for measuring HRQOL in the trial

HRQOL Protocol (2)

- Objectives

- Is the measurement of HRQOL a major (primary) outcome (endpoint) or a secondary endpoint in the study?
- Within the HRQOL scores, will a particular domain be of more interest than another, such as emotional functioning, or will all domains be of equal interest?
- Clearly stated objectives establish the importance of measuring HRQOL in the trial

HRQOL Protocol (3)

- **Eligibility criteria**

- Will patients be required to indicate their willingness to participate and answer questionnaires or to be interviewed at specified times?
- If a patient is not willing or unable to participate in HRQOL assessment, is the patients still eligible for the trial?
- Is a certain level of reading and comprehension required?
- Will oral translation of self-report questionnaires be allowed if a patient does not understand the language in which the questionnaire is written?
- When HRQOL is an endpoint in a trial, there may be eligibility criteria required in addition to those that are normally included in protocols, such as ability and willingness to answer HRQOL questionnaire(s).

HRQOL Protocol (4)

- **Study design**

- Which assessment method will be used, interview or questionnaire?
- How structured will interviews be?
- If questionnaires are used, which instrument(s) will be used?
- When will the assessments be administered?
- Where will HRQOL administration take place, in the clinic or at home? If the latter, will it be conducted by telephone?
- Who will be responsible for administration of the interviews or questionnaires?
- The Interview method is preferable in phase I or II studies, whereas the self-report questionnaires are the method of choice in large phase III clinical trials
- The timing of HRQOL administrations in relation to interventions and the course of the illness trajectory, is very important – a baseline administration before randomization and treatment initiation should be mandatory in all trials

HRQOL Protocol (5)

- **Instrument description**
 - The protocol should contain a brief, but adequate description of the interview method or instrument and a full copy of the questionnaire(s) to be used
 - The anticipated time it will take patients to complete the assessment should be indicated
 - The questionnaire itself is best placed in an appendix to the main protocol
- **Sample size**
 - A clear statement of the sample size required to answer the HRQOL questions in the trial must be given
 - The protocol should contain a clear statement as to why the indicated sample size was chosen and how it was calculated
 - This is mandatory when HRQOL is the primary endpoint

HRQOL Protocol (6)

- **Monitoring, Stopping rules, Evaluation, and Analysis**
 - Will the data be monitored during the course of the trial to determine whether enrollment of patients into the trial should be stopped or otherwise altered? If so, what are the rules for making such a decision?
 - Stopping rules are generally designed to ascertain (1) whether unexpected, serious toxicity has occurred (2) whether the efficacy endpoint(s) in one arm of the trial is or are superior to that of any other to an extent that it is unethical to continue with the study
 - How will the responses in the questionnaires be scored and analyzed?
 - Phase III focus on HRQOL differences between the groups whereas phase I and II studies focus on pre-treatment and post-treatment differences within a group
 - If more than one HRQOL outcome is measured, what is the primary outcome (hypothesis) and how will it be analyzed?
 - How will other HRQOL outcomes be analyzed?

HRQOL Protocol (7)

- **Consent form**

- The consent form should state that HRQOL is being measured and the purpose for which the data will be used
- Whether or not there will be a potential benefit to the participant should be stated
- The number of times that the subject will be required to complete HRQOL assessments and the length of time it will take for each assessment should be given
- A statement as to whether the data are being collected for research purposes only or whether they will be used in the day-to-day care of the patient should be made
- Other standard statements about confidentiality, who will see the data, and the right to refuse to participate or to drop out of the study at any time without jeopardizing future care should be included

HRQOL Protocol (8)

- **Cover sheet for monitoring compliance**
 - In order to reduce missing data and, when this is unavoidable, to provide an explanation for it, a cover sheet for the questionnaire which is to be filled out by study personnel should be attached to the front of the HRQOL questionnaire
- **Instructions for administration**
 - Are detailed instructions provided so that personnel responsible for collecting the HRQOL data are fully aware of the procedures to be followed?
 - How will the data be transmitted to the central office?
 - Will direct electronic entry and transmission be used?
 - Detailed instructions on how to present the HRQOL instruments for completion should be provided for study personnel responsible for the collection of the data

HRQOL Protocol (9)

- **Instructions for administration (cont'd)**
 - Complete instructions should be given about how to return the HRQOL data to the central data processing office
 - Will the data be sent to the office as they are collected, or will they be kept in the participating centre office and sent in batches according to a predefined schedule?
 - Will direct entry, using computers with touch-sensitive video monitors (screens), and electronic transmission be used?
 - Instructions on preserving confidentiality, regardless of the data collection method used, should be given
- **Appendix (to the main protocol)**
 - Details about characteristics of an instrument, the instrument itself with its coversheet, and detailed instructions for the collection of the data can be included in one or more appendices to the main protocol